Decision Memo for Positron Emission Tomography (FDG) for Soft Tissue Sarcoma (STS) (CAG-00099N)

Decision Summary

CMS determines that the evidence is not adequate to conclude that FDG-PET for diagnosing, staging, restaging, or monitoring therapy for STS is reasonable and necessary for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population specified in the request for national coverage. (§1862(a)(1)(A))

Therefore, CMS intends to maintain noncoverage of FDG PET in soft tissue sarcoma.

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Decision Memo

This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction giving specific directions to our claims-processing contractors. That manual issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.

To: File: FDG Positron Emission Tomography (FDG-PET) Soft Tissue Sarcoma (STS) CAG-00099N

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Re: Medicare National Coverage Determination (NCD) on FDG-PET for Soft Tissue Sarcoma – Noncovered Service

Date: April 16, 2003

This memorandum serves four purposes: (1) outlines the background of FDG-PET and soft tissue sarcoma; (2) reviews the history of Medicare coverage and provides a time line of recent activities; (3) presents and analyzes the relevant scientific and clinical data related to FDG-PET for soft tissue sarcoma; and (4) delineates the reasons for noncoverage of FDG-PET for soft tissue sarcoma.

Clinical Background

Soft tissue sarcoma (STS) is a heterogeneous group of malignant tumors that develop in the soft tissues of the body, including muscles, tendons, fat, fibrous tissue, blood vessels, nerves and synovial tissue. This type of cancer is relatively uncommon and accounts for less than 1% of new cancer cases each year. According to the National Cancer Institute, the primary tumor site arises from the extremities (arms, legs, hands or feet) in 50% of cases, the trunk (chest, back, hips, shoulders, and abdomen) in 40% and in the head and neck in 10% of cases. At the time a patient first presents with STS, 10 - 23% will already have metastatic disease. The most common location for metastatic disease is the lung, which is the site for one-third of all secondary tumors.[1] Treatment options for STS are based upon the grade and size of the tumor and the presence of metastases. Therefore, treatment decisions are dependent upon clearly defining the local tumor and tumor spread. Traditional imaging currently used such as magnetic resonance imaging (MRI) and computed tomography (CT) depict the anatomic location and shape of structures in the body whereas FDG-PET, a molecular imaging modality, detects biological activity.

FDG-PET is a noninvasive diagnostic imaging procedure that assesses the level of metabolic activity and perfusion in various organ systems of the human body. Images are obtained from positron-emitting radioactive tracer substances (radiopharmaceuticals) that are usually administered intravenously to the patient. 2-[F-18] Fluoro-D-Glucose (FDG) is an injected radioactive tracer substance that emits sub-atomic particles, known as positrons, as it decays. FDG-PET uses a positron camera (tomograph) to measure the decay of radioisotopes such as FDG. The rate of FDG decay provides biochemical information on glucose metabolism of the tissue. As malignancies can cause abnormalities of metabolism and blood flow, FDG-PET evaluation can indicate the probable presence or absence of malignancy based upon observed differences in biologic activity.

An FDG-PET scan can be interpreted based on qualitative and/or semi-quantitative evaluation. Qualitative FDG-PET involves making assessments by visually interpreting the scan results. Metabolically active areas of the body "light up" on an FDG-PET scan more so than less active areas. Metabolically active areas may include areas of cancer, inflammation, and benign cellular activity. Semi-quantitative evaluation uses the glucose metabolic rate of a tumor and, through computer software, determines a numeric value representing the metabolic activity for that tumor. Tumor-to-background ratio is a semi-quantitative method that compares tumor uptake to surrounding tissue. Standardized uptake value takes into account such factors as patient weight and FDG dosage.

History of Medicare Coverage on FDG-PET for STS

FDG-PET for STS was part of a broad request for coverage of FDG-PET that was received by the Centers for Medicare and Medicaid Services (CMS) in July 2000. At that time, CMS determined FDG-PET was under the diagnostic services benefit category (§1861(s)(3) of the Social Security Act (the Act)) and divided the request into individual indications. Many of these indications were reviewed at that time and, along with previous determinations, combined into CMS's national policy on the use of FDG PET – Coverage Issues Manual (CIM) Section 50-36. Several indications were determined at that time not to be reasonable and necessary under §1862(a)(1)(A) of the Act and not covered. PET for STS is included in the category "All other uses of PET scans not listed in this manual…."

Timeline of Recent Activities

October 18, 2001	CMS formally accepted the request to consider coverage of FDG-PET for STS.
December 10, 2001	CMS referred the issue to the Agency for Healthcare Research and Quality (AHRQ) for a technology assessment (TA).
February 19, 2002	Receipt date of TA was extended.
April 8, 2002	CMS received the final external TA from AHRQ.
June 7, 2002	Due date extended to allow additional time for review.
June 24, 2002	After exhaustive review we have decided to delay announcement of any determination until MCAC has reviewed and made recommendations on reviewing evidence for rare conditions.
September 25, 2002	On September 25, 2002, the MCAC met to discuss assessing evidence for diseases that affect small populations.
November 4, 2002	CMS received the minutes from the September MCAC meeting.

Food and Drug Administration (FDA) Status

The FDA approval letter for new drug application NDA 20-306, dated June 2, 2000 included the following language:

"This new drug application provides for the use of Fluorodeoxyglucose F-18 injection for the following indications:

Assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer…. We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter….[2]"

Benefit Category

In the preamble to a final rule published on November 1, 2002, CMS noted:

Section 1861(t)(1) provides that the terms drugs and biologicals ''include only such drugs (including contrast agents) and biologicals, respectively, as are included (or approved for inclusion) in [one of several pharmacopoeias] (except for any drugs and biologicals unfavorably evaluated therein), or as are approved by the pharmacy and drug therapeutics committee (or equivalent committee) of the medical staff of the hospital furnishing such drugs and biologicals for use in such hospital.'' A careful reading of this statutory language convinces us that inclusion of an item in, for example, the USPDI … does not necessarily mean that the item is a drug or biological. Inclusion in such reference (or approval by a hospital committee) is a necessary condition for us to call a product a drug or biological, but it is not enough. Rather, if we are to call a product a drug or a biological for our purposes, CMS must still make its own determination that the product is a drug or biological…[3]

The appropriate benefit category for all diagnostic radiopharmaceuticals is 1861(s)(3). We will consider neither diagnostic nor therapeutic radiopharmaceuticals to be drugs as described in section 1861(t).[4]

Summary of Evidence

Technology Assessment (TA)

CMS requested assistance from AHRQ to perform a TA on the use of FDG-PET to diagnose, grade and manage STS. The TA can be reviewed at http://www.cms.hhs.gov/ncdr/tadetails.asp?id=69. The TA search strategies, selection criteria, and other methodological aspects can be obtained from the TA directly. The following questions were formulated by AHRQ for this report:

1. What is the diagnostic test performance (sensitivity and specificity) of FDG-PET for:

   a. Distinguishing benign lesions from malignant STS?
   b. Distinguishing low-grade from high-grade STS?

2. How does the test performance of FDG-PET compare with conventional anatomic imaging (CT, MRI, etc.) among patients with STS with respect to:

   a. Primary diagnosis?
   b. Diagnosing locoregional recurrence?
   c. Diagnosing distant metastasis?

3. A review of studies on changes in patient management or improved outcomes for patients with STS with the use of FDG-PET.

4. A review of studies on using FDG-PET to determine tumor response to therapeutic interventions for patients with STS.

CMS staff also conducted an internal technology assessment utilizing the same questions. There were some differences in retrieval from the external TA based upon individualized search strategies of the respective evaluations. The external TA included the 12 articles retrieved by CMS (Appendix A) and 8 additional articles. The 12 articles jointly reviewed were the pertinent diagnostic articles. Consequently, the ensuing review of the literature reflects a synthesis of CMS staff work and the external TA results.

However, one point of departure is noted. Although the external TA discusses semi-quantitative and quantitative FDG-PET, CMS analysis focused on visualized (qualitative) FDG-PET. There are two key reasons for this: (1) Practicing nuclear medicine physicians do not routinely use quantitative methods during the course of daily practice; and (2) The current body of evidence on semi-quantitative FDG-PET lacks specific standards for collecting, analyzing, and interpreting data. Since these articles did not use consistent standards for their semi-quantitative data, we were unable to compare data across articles or make generalizations regarding the diagnostic value of semi-quantitative FDG-PET. Quantitative FDG-PET, which is based upon complex pharmacokinetic calculations, is even more remotely related to day-to-day nuclear medicine practice. Therefore, CMS did not review quantitative FDG-PET data.

Question 1.a. – Can FDG-PET distinguish benign lesions from malignant STS?

The article written by Schulte[5] is a prospective study of 102 patients (55 male, 47 female, median age 49 years, range 1-89). Eighty-eight had a suspected primary diagnosis of STS. A histologic gold standard was available for all cases. That is, a tissue biopsy was performed and was used as an independent truth standard against which the FDG-PET results were compared. (Note that the presence of an independent gold or truth standard is fundamental to defining the two key performance parameters of any type of diagnostic test: sensitivity and specificity.) The sensitivity of FDG-PET (i.e., the percentage of patients with histologically-proven STS who have a positive FDG-PET scan) was 97% (95% confidence interval (CI) 90-100%), and the specificity (i.e., the percentage of patients without histologically proven STS who have a negative PET scan) was 65.7% (CI 48-81%). However, it was not possible to exclude pediatric patients or recurrent lesions (n = 14) when calculating sensitivity and specificity. Furthermore, there remains a question of how the sensitivity and specificity values were calculated since the study appeared to have its FDG-PET scan results partially dependent upon histologic findings, when, in fact, the proper computation of such values requires separate interpretation of FDG-PET and tissue findings.

Lucas, 1999,[6] prospectively assessed 30 consecutively recruited patients (mean age 51, range 6-85) who presented with soft tissue masses that were considered to be malignant after clinical examination and MRI. A histological gold standard was available for all cases. Exclusions could not be made for pediatric cases in the data analysis. Qualitative interpretation of FDG-PET resulted in a sensitivity of 94.7% and a specificity of 58.3%.

Watanabe[7] is a diagnostic trial of 55 patients (26 male, 29 female) who had been referred for clinical evaluation of bone and soft tissue tumors. Data were available for 34 adult soft tissue lesions. A histologic gold standard was available in all cases except for one hematoma. The sensitivity of FDG-PET was 100% and the specificity was 26%.

Nieweg[8] included 22 patients (13 male, 9 female, mean age 50 years, range 18-82) who had suspected malignant soft tissue lesions based upon initial clinical findings. A histologic gold standard was available for all cases. Visual interpretation of FDG-PET revealed a sensitivity of 100%, and a specificity of 75%. Note that selection bias is a consideration when a study such as this one only recruited cases with a high *a priori* suspicion of malignancy, therefore possibly inflating test sensitivity. Since sensitivity measures the number of patients with a positive test who actually have the disease, choosing patients who most likely have the disease will obviously have the potential of inflating that result.

Ferner[9] and Schwarzbach[10] also provided study data regarding primary lesions (with at least a sample size of 10 patients) where the sensitivity/specificity in Ferner was 100%/86% and Schwarzbach was 91%/88%. Four studies regarding recurrent lesions (with at least a sample size of 10 patients) demonstrated a sensitivity ranging from 50–100%, and specificity from 92–100%. Lucas, 1998[11] was the largest of these four diagnostic accuracy studies, with 62 patients and 72 scans (sensitivity 74% and specificity 94%).

Question 1.b. – Can FDG-PET distinguish low-grade from high-grade STS?

Data from several small studies (Schwarzbach[12], Lucas 1999[13], Schulte[14], Nieweg[15] and Kole[16]) were not able to differentiate rates of visualization between Grade II/III STS and Grade I STS. However, when benign lesions were factored in, rates of visualization tended to be lower (no tests of statistical significance performed) for such benign lesions. Only the study by Kole[17] studied recurrent lesions alone, whereas the others involved primary lesions. Also, these data were somewhat different from the semi-quantitative data (i.e., standard units of tracer uptake are plotted on a graph according to severity or grade of tumor) in which Grade II/III lesion data points showed fairly good separation from both Grade I and benign lesions. However, Grade I and benign lesion data points are not readily distinguished from one another.

Question 2.a. – How does FDG-PET compare with conventional anatomic imaging for detecting primary lesions?

No studies were available to address this question.

Question 2.b. – How does FDG-PET compare with conventional anatomic imaging for detecting locoregional recurrent lesions?

In Lucas, 1998,[18] discussed above, there was a sensitivity of 74% and a specificity of 94% for locoregional recurrence. These values compared to MRI, which had a sensitivity for local site recurrence of 88% and a specificity of 96%. Although the sensitivity of MRI appears higher, there is no statistically significant difference. Also, this study is subject to some degree of verification bias since it was unclear if biopsies were performed in all cases. The absence of a biopsy prevents the 'verification' of the accuracy of the scan.

Kole[19] reported on a series of 17 patients, of whom 15 had STS. FDG-PET had a sensitivity of 93% (14/15), compared to 77% (10/13) for MRI (MRI was not performed in two cases). With only 2 non-STS patients, specificity calculations cannot be reliably performed.

Question 2.c. – How does FDG-PET compare with conventional anatomic imaging for detecting metastatic lesions?

Lucas, 1998[20] was also the only accessed article that directly studied metastatic disease. The study compared FDG-PET to CT of the chest among the 62 patients (34 male, 28 female, mean age 50 years, range 2-83) who were being evaluated for lung metastases. Although in 9 patients, FDG-PET identified extra-pulmonary sites of high metabolic activity, there were no available data for which sensitivity/specificity values could be calculated. With respect to lung data, it was not clear what type of independent gold standard was uniformly in place since only an unspecified number of patients had tissue diagnoses. FDG-PET had a sensitivity of 86.7% and specificity of 100%, compared to CT of the chest with a sensitivity of 100% and specificity of 96.4%. Furthermore, pediatric cases could not be excluded from the reported data.

Other studies by Lucas, 1999[21] and El-Zeftawy[22] provided descriptive comparisons without computed sensitivity and specificity values. Neither provided evidence of the incremental value of PET over CT or MRI.

Question 3 – Can the use of FDG-PET change patient management or improve outcomes for patients with STS?

No randomized or other controlled studies addressed these questions. Four studies, the largest of which is briefly described below under Question 4, presented anecdotal information on this issue.

Question 4 – Can the use of FDG-PET determine tumor response to therapeutic interventions for patients with STS?

Of the 4 small studies on this issue, only 1 by van Ginkel[23] had a sample size exceeding 10 patients. In this series of 20 patients with locally advanced primary (n = 14) or recurrent (n = 6) sarcoma, 7 showed complete response (no residual tumor) and 12 showed partial response (with residual tumor) on pathological examination (1 patient was excluded) after treatment. Glucose consumption, rather than FDG-PET visualization, was the metric utilized, and the authors concluded: "FDG-PET indicated the pathologic tumor response to hyperthermic isolated limb perfusion, although the lack of specificity of FDG, in terms of differentiating between an inflammatory response and viable tumor tissue, hampered the discrimination between partial and complete response." Given the very specific therapeutic modality used, this study has a questionable generalizability.

External TA Summary

- FDG-PET has good ability to evaluate both primary and recurrent soft tissue lesions but is unable to distinguish between low-grade tumors and benign lesions.
- The limited data suggest approximately similar diagnostic performance of FDG-PET and MRI for detecting locoregional recurrence; however, there are too few patients studied to draw reliable conclusions.
- There is insufficient data on the impact of FDG-PET on clinical outcomes and on the usefulness of FDG-PET in assessing the response to therapy.

MCAC

On September 25, 2002, the MCAC Executive Committee (EC) met to discuss assessing evidence for diseases that affect small populations. As indicated previously, STS is a disease that affects a small population. Minutes and complete transcripts from the meeting are available on our website at http://www.cms.hhs.gov/mcac/default.asp. The MCAC recommended that, even for diseases that affect small populations of patients, Medicare coverage should still be based on solid, scientific evidence.

Position Statements

There were no position statements or professional guidelines located by CMS or AHRQ that addressed the use of FDG-PET for STS. No public comments or letters of support were submitted.

CMS Analysis

NCDs are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Act (§1869(f)(1)(B)). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, in general, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member" (§1862(a)(1)(A) of the Act).

CMS issued regulations pertaining to the coverage of diagnostic tests under the Part B program. Those rules provide, with few exceptions, that diagnostic tests must be ordered by the physician who treats the beneficiary for a specific medical problem and the physician must use the results in the management of that medical problem (42 C.F.R. §410.32). In general, tests not ordered by the treating physician are not considered to be reasonable and necessary (42 C.F.R. §411.15(k)(1)).

Given the above body of evidence for STS and FDG-PET, CMS created an analytical framework (Appendix B) for addressing specific issues about the applicability of FDG-PET at different points along the continuum of care for STS. Below, the analysis of FDG-PET for STS is broken down into fundamental questions, which are based upon this analytical framework.

A. Is FDG-PET appropriate for initial diagnosis in place of biopsy?

Sensitivity values in the pertinent studies ranged from 74-97% and specificity ranged from 26-94%. In addition, the results of many studies included patients with initial, recurrent, and metastatic lesions that could not be isolated in the analysis.

Histopathic tissue diagnosis (biopsy) is currently the most accurate method of diagnosing malignancy. Many of the studies reviewed in this document used histopathologic diagnosis as their gold standard in comparing FDG-PET results. The evidence shows that FDG-PET is not as accurate a diagnosis tool as biopsy. Since the PET performance data fell short of the biopsy gold standard, PET cannot be considered to serve as an alternative modality for initial diagnosis since many cancers would be inaccurately diagnosed. Thus, in this particular clinical application, evidence is insufficient to support clinical utility of FDG-PET.

There are no professional guidelines concerning the use of FDG-PET for this application.

B. Can FDG-PET help to distinguish between different pathologic states, given biopsy results that either:
1.Cannot establish a tumor as malignant vs. benign? or,
2.Cannot grade a malignant tumor?

The external TA evidence suggests that FDG-PET is not able to consistently distinguish low-grade malignant tumors from benign lesions. In addition, there is poor separation of intermediate/high-grade tumors from low-grade tumors using qualitative data. The better separation of different tumor grades achieved by semi-quantitative data has unclear significance given the issues discussed above surrounding the application of semi-quantitative data to actual nuclear medicine practice. In addition, there are no professional guidelines concerning FDG-PET for this indication. In summary, FDG-PET is not able to diagnose or grade a malignancy with the accuracy of a biopsy. Thus, in this particular clinical application, evidence is insufficient to support clinical utility of FDG-PET.

C. For initial staging and restaging, can FDG-PET aid in directing patient management by effectively detecting metastatic disease?

There is limited available evidence on FDG-PET and anatomic imaging. A single article from Lucas, 1998[24] addresses pulmonary lesions with respect to both imaging modalities. However, the article lacks critical information on what type of gold standard was in place for the study and how many patients had their FDG-PET scan results verified with histologic diagnoses. The external TA analysis is that this study's trends suggest that FDG-PET and anatomic imaging perform equally. However, the poor quality design of this study does not allow definitive conclusions to be drawn about the equivalency of their performance. We agree with that determination. There are also no specialty society guidelines or expert opinion that support the use of FDG-PET for this indication. Therefore, evidence is insufficient to support the clinical utility of FDG-PET for this indication.

D. Can FDG-PET impact patient management by evaluating tumor response to preoperative therapy where chemotherapy and/or radiation therapy is used?

There is limited, non-generalizable evidence in this area (also reported in the external TA) that prevents any conclusion of the utility of FDG-PET for this particular indication. The only available trial studied hyperthermic isolated limb perfusion and used semi-quantitative analysis rather than visualization to determine response to therapy. This information on the specialized hyperthermic isolated limb perfusion method does not provide a more generalizable body of evidence on how preoperative management might be conducted. In addition, semi-quantitative PET is not standardized so as to be a consistently valid interpretative tool. Therefore, in this clinical indication, evidence is insufficient to support the clinical utility of FDG-PET.

E. For restaging, is FDG-PET an effective means for diagnosing locoregional recurrence?

Lucas, 1998[25] discussed under staging and restaging above, is again the only article that compares FDG PET to anatomical imaging for diagnosing locoregional recurrence. It also suggests equivalence between the tests but, again, its poor quality does not allow definitive conclusions about the equivalency of their performance. Specialty society guidelines and expert opinion were not available supporting this indication.

Decision

CMS determines that the evidence is not adequate to conclude that FDG-PET for diagnosing, staging, restaging, or monitoring therapy for STS is reasonable and necessary for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population specified in the request for national coverage. (§1862(a)(1)(A))

Therefore, CMS intends to maintain noncoverage of FDG PET in soft tissue sarcoma.

Appendix A

CMS performed a literature search using PubMed, located on the National Library of Medicine web site. Our selection criteria were minimally restrictive given the rarity of STS and the fact that relatively few published articles are available. However, the articles most valuable to the internal CMS review included the sensitivity and specificity of diagnostic trial data based on qualitative data; the isolation of pediatric cases; and identification of quantitative data suggestive of histologic grading.

PubMed was searched using the term "soft tissue sarcoma" AND "FDG PET" resulting in 50 articles. After limiting the results to articles in English and human subjects, 39 articles were obtained.

Another PubMed search was performed using the terms "soft tissue sarcoma" AND "positron emission tomography" with the limits human and English. Other PubMed searches were executed using the following search terms, in order to make the search more histology-specific.

- Liposarcoma AND FDG PET
- Leiomyosarcoma AND FDG PET
- Rhabdomyosarcoma AND FDG PET
- Malignant schwannoma AND FDG PET
- Neurofibrosarcoma AND FDG PET
- Neurogenic sarcoma AND FDG PET
- Ewing's sarcoma AND FDG PET
- Primitive neuroectodermal tumor AND FDG PET
- Synovial sarcoma AND FDG PET
- Hemangiosarcoma AND FDG PET
- Lymphangiosarcoma AND FDG PET
- Kaposi's sarcoma AND FDG PET
- Dermatofibrosarcoma protuberans AND FDG PET
- Angiosarcoma AND FDG PET
- Fibrosarcoma AND FDG PET
- Malignant fibrous histiocytoma AND FDG PET
- Hemangiopericytoma AND FDG PET
- Malignant mesenchymoma AND FDG PET
- Epithelioid sarcoma AND FDG PET
- Clear cell sarcoma AND FDG PET
- Desmoplastic small cell tumor AND FDG PET
- Hemangioendothelioma AND FDG PET

Another search was performed using the following search terms:
FDG-PET OR fluorodeoxyglucose OR positron emission tomography OR PET or deoxyglucose OR FDG OR fluoro-2-deoxy-D-glucose AND **Liposarcoma OR leiomyosarcoma OR rhabdomyosarcoma OR malignant schwannoma OR neurofibrosarcoma OR neurogenic sarcoma OR Ewing's sarcoma OR primitive neuroectodermal tumor OR synovial sarcoma OR hemangiosarcoma OR lymphangiosarcoma OR Kaposi's sarcoma OR dermatofibrosarcoma protuberans OR angiosarcoma OR fibrosarcoma OR malignant fibrous histiocytoma OR hemangiopericytoma OR malignant mesenchymoma OR epithelioid sarcoma OR clear cell sarcoma OR desmoplastic small cell tumor OR hemangioendothelioma.**

Results from all searches were compiled and duplicates were eliminated.

CMS search results:

Dimitrakopoulou-Strauss A, Strauss LG, Schwarzbach M, et al. Dynamic PET 18-F-FDG studies in patients with primary and recurrent soft-tissue sarcomas: impact on diagnosis and correlation with grading. *Journal of Nuclear Medicine* 2001;42:713-720.

Eary JF, Conrad EU, Bruckner JD, et al. Quantitative [F-18] fluorodeoxyglucose positron emission tomography in pretreatment and grading of sarcoma. *Clinical Cancer Research* 1998;4:1215-1220.

Folpe AL, Lyles RH, Sprouse JT, et al. (F-18) fluorodeoxyglucose positron emission tomography as a predictor of pathologic grade and other prognostic variables in bone and soft tissue sarcoma. *Clinical Cancer Research* 2000;6:1279-1287.

Kern KA, Brunetti A, Norton J, et al. Metabolic imaging of human extremity musculoskeletal tumors by PET. *Journal of Nuclear Medicine* 1988;29(2):181-186.

Lodge MA, Lucas JD, Marsden PK, et al. A PET study of 18-FDG uptake in soft tissue masses. *European Journal of Nuclear Medicine* 1999;26(1):22-30.

Lucas JD, O'Doherty MJ, Wong JC, et al. Evaluation of fluorodeoxyglucose positron emission tomography in the management of soft-tissue sarcomas. *The Journal of Bone and Joint Surgery (Br)* 1998;80-B(3):441-447.

Lucas JD, O'Doherty MJ, Cronin BF, et al. Prospective evaluation of soft tissue masses and sarcomas using fluorodeoxyglucose positron emission tomography. *British Journal of Surgery* 1999;86:550-556.

Nieweg OE, Pruim J, van Ginkel RJ, et al. Fluorine-18-fluorodeoxyglucose PET imaging of soft-tissue sarcoma. *Journal of Nuclear Medicine* 1996;37:257-261.

Schwarzbach MH, Dimitrakopoulou-Strauss A, Willeke F, et al. Clinical value of [18-F] fluorodeoxyglucose positron emission tomography imaging in soft tissue sarcomas. *Annals of Surgery* 2000;231(3):380-386.

Shulkin BL, Mitchell DS, Ungar DR, et al. Neoplasms ion a pediatric population: 2-[F-18]-fluoro-2-deoxy-D-glucose PET studies. *Radiology* 1995;194:495-500.

van Ginkel RJ, Hoekstra HJ, Pruim J, et al. FDG-PET to evaluate response to hyperthermic isolated limb perfusion for locally advanced soft-tissue sarcoma. *Journal of Nuclear Medicine* 1996;37:984-990.

Watanabe H, Shinozaki T, Yanagawa T, et al. Glucose metabolic analysis of musculoskeletal tumours using 18-fluorine-FDG PET as an aid to preoperative planning. *The Journal of Bone and Joint Surgery (Br)* 2000;82-B:760-767.

Appendix B

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1 Lucas JD, et al. 1998.

2 Letter from Patricia Love, FDA, to Downstate Clinical PET Center. June 2, 2000. This letter is available on the FDA web site through a link at http://www.fda.gov/cder/approval/index.htm.

3 67 Federal Register 66757

4 67 FR 66757

5 Schulte M, et al. 1999

6 Lucas JD, et al. 1999

7 Watanabe H, et al. 2000

8 Nieweg OE, et al. 1996

9 Ferner RE, et al. 2000

10 Schwarzbach MH, et al. 2000

11 Lucas JD, et al. 1998

12 Schwarzbach MH, et al. 2000

13 Lucas JD, et al. 1999

14 Schulte M, et al. 1999

15 Nieweg OE, et al. 1996

16 Kole AC, et al. 1997

17 Ibid

18 Lucas JD, et al. 1998

19 Kole AC, et al. 1997

20 Lucas JD, et al. 1998

21 Lucas JD, et al. 1999

22 El-Zeftawy H, et al. 2001

23 van Ginkel RJ, et al. 1996

24 Lucas JD, et al. 1998

25 Ibid.

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